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Reply

Ethnic Diversity and Immunological Barriers in Heart Transplantation

We appreciate the interest shown by Dr. Deutsch and colleagues in our work (1) and their thoughtful comments regarding outcomes after heart transplantation (HT) as a function of race, panel reactive antibody (PRA) burden, and sensitization. We agree that existing data suggest the superiority of tacrolimus-based immunosuppressive regimens, particularly in black patients (2), with the proviso that blacks often require higher tacrolimus doses to reach therapeutic trough concentrations (3,4). Importantly, a recent analysis from the United Network for Organ Sharing (UNOS) database shows that a higher proportion of black HT recipients were receiving tacrolimus therapy than whites in recent years (5). We did not investigate differences in the use of various induction strategies, but previous studies have shown that induction immunosuppression using lymphocytolytic agents in the early perioperative period was associated with a survival benefit in younger black patients with ≥4 human leukocyte antigen (HLA) mismatches (6).

Dr. Deutsch and colleagues also correctly noted the insensitivity of standard Centers for Disease Control and Prevention (CDC)-based PRA testing compared to newer solid-phase or microsphere-based assays that have been increasingly used since the mid-1990s (7). Specific information regarding the technique used for HLA antibody detection was however not available in the UNOS database. To partially circumvent this issue, we limited our analysis to transplantations that were performed after 2000, hoping to capture the PRA results that were largely based on newer HLA platforms. Recent consensus guidelines in this regard published by the Transplantation Society provide state-of-the-art guidance in the clinical application of newer methods for HLA antibody detection when used in conjunction with conventional methods (8).

Clinical studies that further investigate the results of our study incorporating specific information on the various induction and maintenance immunosuppressive regimens used and the immunologic assays performed for assessment of sensitization status will be of great interest.

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Carotid Plaque Hemorrhage on Magnetic Resonance Imaging and Recurrent Cerebrovascular Events

We read with interest the recent report by Saam et al. (1) describing the predictive value of magnetic resonance imaging–detected carotid plaque hemorrhage for cerebrovascular events. They undertook a meta-analysis of the published research through September 2012 assuming a constant event rate during follow-up to derive an estimated hazard ratio for magnetic resonance imaging–detected carotid plaque hemorrhage of 5.69 (95% confidence interval: 2.98 to 10.87).

Unfortunately, the investigators missed our most recent work (2), which included a meta-analysis and presented new combined data from 3 previous studies (3–5) with increased length of follow-up. We derived a broadly similar conclusion but preferred to report the odds ratio, because the assumption of a constant event rate is unlikely to be true. We found no significant heterogeneity between the studies included ($p = 0.26$, $I^2 = 22.3\%$). The "trim and fill" method (6) was applied to calculate the number of studies that would be required to return the plot to "symmetry" and remove publication bias and to provide a revised estimated odds ratio.

We also note that an assumption was made by the investigators to treat the results from Kume et al. (7) as asymptomatic, despite the investigators' acknowledging that almost one third were symptomatic. It would seem, without further data from Kume et al.'s study, that these results should only be included in a combined meta-analysis for the symptomatic and asymptomatic carotid arteries and should be excluded from the meta-regression. Repeating the meta-analysis including the data from Kume et al., we found an odds ratio at 7.87 (95% confidence interval: 4.7 to 13), but no heterogeneity. Whether or not symptom status affects the relative risk remains unclear, as only 2 studies reported on asymptomatic patients only.

Interestingly, in the past few months, a number of further confirmatory studies have been published, highlighting the importance of this area of research but unsuitable for inclusion in a meta-analysis. More studies are needed for meta-regression to establish effects of symptoms and degree of stenosis. We strongly welcome the suggestion of Saam et al. (1) of harmonization of future studies with respect to randomized controlled trials of this noninvasive marker for stroke and transient ischemic attack.

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Reply

Carotid Plaque Hemorrhage on Magnetic Resonance Imaging and Recurrent Cerebrovascular Events

We thank Dr. Hosseini and colleagues for their thoughtful comments on our recently published meta-analysis on the predictive value of carotid plaque hemorrhage by magnetic resonance imaging on cerebrovascular events (1). We are delighted to observe recently emerging research efforts providing ever more insights into the prognostic role of carotid plaque features by magnetic resonance imaging (2), including the work by Hosseini et al. (3) and others (4,5), which was published after the completion of our report.

Dr. Hosseini and colleagues suggest that utilization of odds ratios might be preferable to hazard ratios (HR) as a means of pooling prognostic data, given that the event rate may not be constant. Although both estimates represent risks associated with distinct findings (i.e., plaque hemorrhage on magnetic resonance imaging), we agree that the most appropriate application of each is dependent on the included source data. In contrast to odds ratios, however, HRs accommodate differences in observation times between studies and censoring and thus are particularly suited for time-to-event analyses (6). In fact, differences in observation times and pattern of censoring were likely to occur in our setting given a median follow-up time of 19.6 months with a range of 1.1 to 38.2 months. Thus, the majority of pooled source populations reported HRs as their primary risk estimate, clearly relying on the proportional hazards assumption over time. In our opinion, both markers of risk suffer from inherent limitations, and future efforts should include more complex statistical approaches such as individual patient–based meta-analyses, which may be more appropriate to determine differences among patient subgroups.

Dr. Hosseini and colleagues argue that the study by Kume et al. (7) should not have been included in the meta-regression analysis comparing differences between symptomatic and asymptomatic subjects. A priori, this study was categorized as an asymptomatic population because of the larger proportion of asymptomatic subjects (68%), but we agree that this assumption is debatable and may warrant specific subanalysis. To accommodate the comments of Dr. Hosseini and colleagues, we excluded the data from that study (7) and incorporated the additional findings of studies published after the completion of our meta-analysis in symptomatic (3) and asymptomatic (4) subjects. Another recent study in asymptomatic subjects was not included, because the authors did not use fat suppression on T1-weighted sequences, which was a predefined inclusion requirement in our meta-analysis (5). Although HRs for the predictive value of carotid plaque hemorrhage on cerebrovascular events were higher in symptomatic (HR: 11.60; 95% confidence interval: 2.88 to 46.63; $p = 0.0006$) compared with asymptomatic (HR: 4.44; 95% confidence interval: 2.54 to 7.76; $p < 0.0001$) subjects, the interaction between the 2 groups did not reach statistical significance. The I^2 value as well as visual inspection of the forest plot indicated heterogeneity similar to our initial analysis ($I^2 = 55.8\%$). Thus, our updated findings are in line with Hosseini et al.'s observation that, on the basis of currently available data, no definite conclusions can be drawn on predictive value in symptomatic compared with asymptomatic patients, and further, more dedicated research is required. It will be interesting to observe whether known underlying differences in the biology of carotid lesions in symptomatic and asymptomatic subjects (8) will eventually translate into clear differences in risk.

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